The Dioxin Toxic Equivalency Factor (TEF) Evaluation: Recap and Update

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Outline

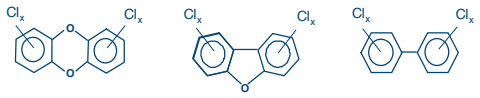
- Overview of the TEF Evaluation studies
  - Aims
  - Recap on data from TCDD, PCB126, PeCDF and TEF mixture studies
  - Update on testing of TEF concept
- Data and carcinogenicity calls only for PCB studies
  - PCB 126: PCB118
  - PCB 153
  - PCB126: PCB 153

Human exposure and TEFs

- Humans are exposed constantly to dioxin-like compounds (DLCs) found in the environment
- Long half-lives lead to persistent exposure
- Toxic equivalency factors (TEFs) developed for risk assessment of human exposure to DLCs

Toxic Equivalency Factors (TEFs)

- A risk assessment tool
- Used for estimating exposure to mixtures of “dioxins”
- Single potency factor relative to 2,3,7,8-TCDD
- Calculate index chemical equivalent dose (ICED)
- Total equivalents (TEQ) =
  ∑([individual “dioxin”] x respective TEF)

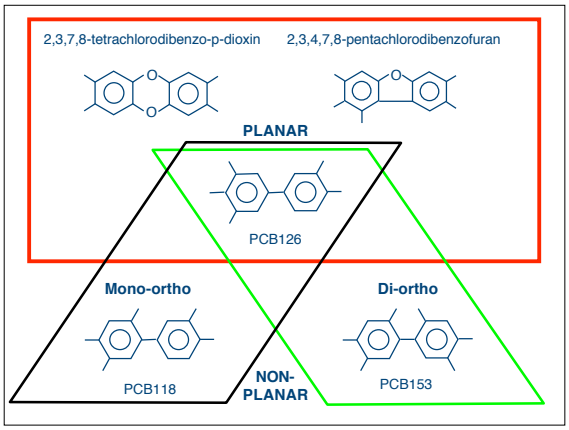


Key assumptions in use of TEFs

- Similar mode of action via the AHR
  - Expect same biological responses as TCDD.
- Parallel dose-response curves
  - Potency varies, not efficacy.
- Relative potency is the same for all endpoints
- Dose-additivity predicts effects for mixtures
  - Add potency adjusted masses to get TEQ
  - TEQ x TCDD response = response for a mixture
- TEF concept nominated for study to the NTP
- Based on administered dose

The NTP Dioxin TEF Evaluation

- A program of eight rodent cancer studies
  - Female rats; 5 days/wk for 2 years
  - Multiple doses, times, CYPs, THs, tissue dosimetry
- Selected Compounds
  - TCDD; TEF = 1.0
    - Index compound
  - PeCDF; TEF = 0.5
    - Most potent PCDF
  - PCB 126; TEF = 0.1
    - Most potent planar PCB and biggest contributor to human TEQ
  - PCB 118; TEF = 0.0001
    - Mono ortho PCB that contributes most to human TEQ in its class
  - PCB 153; no TEF
    - Highest abundance PCB in human tissues on a mass basis



Hypotheses to test

- Testing the TEF concept for carcinogenicity
  - Are the shapes of the dose response curves the same
  - Are the effects seen for a mixture dose additive
- Testing WHO TEFs
  - Effect for a TEQ mixture same as TCDD alone
- Testing interactions between different classes of PCBs

Study Conduct

- Female Harlan Sprague-Dawley rats only
  - Oral, 5 days/wk, corn oil:acetone (99:1) vehicle - 2.5 ml/kg
- Interim studies at 14-, 31-, 53- weeks
  - Histopathology
  - P450, thyroid hormones, tissue dosimetry, hepatocyte replication
- 2-year
  - Histopathology
  - Tissue dosimetry
- Consistent pathology review
  - Same lab-, QA-, and study pathologists, PWG chair, and most of PWG
  - 2nd PWG to reevaluate hepatocellular proliferative lesions across studies
  - Expert advisory panel provided additional guidance on diagnostic criteria for hepatocellular proliferative lesions

Analysis and reporting strategy

- Individual studies-Technical reports
  - No formal **quantitative** comparisons to other studies conducted as part of the TEF Evaluation program.
- Interstudy analyses-Peer reviewed publications
  - Focus on specific issues and hypothesis testing
- Planned NTP "special" reports of interstudy analyses
  - Potential for impact of conclusion on policy for other agencies
  - Need for broad NTP review of analyses and conclusions

Update: TEF Evaluation reporting

- R03 Grantees
  - 5 peer-reviewed publications
- February TR meeting
  - TCDD, PCB126, PeCDF and TEF mixture
- Since last TR meeting
  - 7 NIEHS authored peer-reviewed publications
  - 6 publications currently in preparation

Data recap: Core TEF studies

- TCDD, PCB 126, PeCDF, and TEF mixture
- Expected increases in dioxin responses
  - Increases in CYP1 expression at all doses in all studies
  - Lower T4 and increased T3 for all studies
  - Increased TSH at early time points for TCDD and PCB126
- Hepatotoxicity
  - Dose and duration dependent increase in incidence and severity
- Non-neoplastic effects in multiple organs
- Increased incidence of neoplasms in multiple organs
  - Liver- cholangiocarcinoma and hepatocellular adenoma
  - Lung- cystic keratinizing epithelioma
  - Oral Mucosa- squamous cell carcinoma

Studies compared

Neoplasm	TCDD	PCB126	PeCDF	Mix
Cholangiocarcinoma	+++	+++	++	+++
Hepatocellular adenoma	+++	++	++	+++
Cystic kerat. epithelioma	+++	+++	+	+++
Oral Mucosa - Sq cell carco	++	+++	++	
Uterus - Sq. cell carcinoma	++			
Pancreas- Ad/carcinoma	+		+	+
Cholangioma	+	+		
Hepatocholangioma	+	++		
Lung - Sq cell carcinoma		+++		
Uterus-adenoma/carcinoma			+	
Adrenal Cortex -Ad/carco		+		

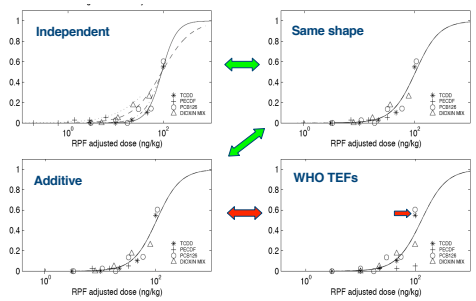
Specific hypotheses

- Site specificities of carcinogenicity are the same
- Shape of dose response curves for a given site are the same across compounds/mixtures
- Effects seen for mixtures are dose additive based on constituents effects and individual potencies
- Relative potencies for a given endpoint/site and WHO TEFs are the same
- Effects seen for mixtures are dose additive based on constituents effects and WHO TEFs

Testing the TEF Hypotheses

- Dose response models of four core studies
  - TCDD, PeCDF, PCB126 and TEF mixture
- Administered dose for all tests
- Modeled under 4 different parameter conditions
  - Independent model
  - Same shape model (differ by ED_{50} only)
  - Additive model
    - ED_{50} Mixture = ED_{50} (TCDD)
  - WHO model using WHO TEFs
    - PCB126 = 0.1, PeCDF=0.5
- Use likelihood ratio tests to compare model fits

Model fits-cholangiocarcinoma



General findings -Cancer data

- Evaluating same shape dose response curves
  - Non-linear behavior
  - Cannot reject they have same shape
- Dose additive model for the mixture
  - Cannot reject at p<0.01
- WHO model
  - Cannot reject for hepatocellular adenoma and gingival squamous cell carcinoma
  - Can reject for cholangiocarcinoma and Lung-CKE

Walker NJ, Crockett P et al (2004) Dose-additive carcinogenicity of a defined mixture of "dioxin-like compounds". Environ Health Perspect: doi:10.1289/ehp.7351.

General findings -Interim P450 data

- Non parallel dose response curves
  - Significantly different shape at all time points
- Mixture responses were sometimes additive.
  - Had to force models to have same shape to do this.
  - Only additive for
    - CYP1A1-14 weeks
    - CYP1A2-53 weeks
- WHO model
  - Rejected at all time points
- Did not test dose additivity with varying efficacy

Toyoshiba H, Walker NJ et al (2004) Evaluation of toxic equivalency factors for induction of cytochromes P450 CYP1A1 and CYP1A2 enzyme activity by dioxin-like compounds. Toxicol Appl Pharmacol 194(2):156-68

Potency Factors close to TEF values

	PCB126	PeCDF	TEF Mixture
WHO TEF	0.1	0.5	(1.0)
Cholangiocarcinoma	0.11	0.16	0.98
Hc adenoma	0.10	0.35	1.02
Lung CKE	0.19	0.34	1.21
Gingival SCC	0.09	0.24	0.467
CYP1A1	0.02 - 0.19	0.1 - 0.44	0.63 - 2.27
CYP1A2	0.17 - 0.51	0.17 - 0.47	0.51 - 0.80

Messages to take home

- First studies to test "TEF concept" for cancer
  - Same patterns of cancer response
  - Support for dose additivity for administered dose
  - General support of TEF method for rodent cancer
    - Use of TEF method by EPA under review by NAS
- Suggested reevaluation of TEF value of PeCDF
  - WHO expert panel to convene in 2005
- Current TEF scheme based on administered dose
  - Need for RPFs based on internal dose metrics
  - Complex issue due to AhR ligand pharmacokinetics
    - Liver sequestration due to binding to CYP1A2

Ongoing analyses

- TEF Hypothesis testing for non neoplastic lesions
  - Interim time points and 2 year
- TEF Hypothesis testing based on other dose metrics
  - Measured metrics
    - Tissue dose, total body burden
  - Non measurable metrics
    - Non CYP1A2 bound ligand
    - AhR-ligand
- AhR PBPK model of the mixture
  - Based on additive combination of TCDD, PeCDF and PCB126 models
  - Work in progress

Next phase: PCB studies

- PCB153
  - Highest abundance PCB in human tissues on a mass basis
  - Not in TEF scheme
- PCB126:PCB153 mixture
  - Interaction between non-ortho and di-ortho PCBs
- PCB126:PCB118 mixture
  - Additivity of non-ortho and mono ortho PCBs
- PCB118-to be reported in 2008?
  - Highest abundance mono ortho PCB in human tissue
  - Highest TEQ contributor of mono ortho class in TEF scheme